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Central Nervous System Involvement in Children with Sarcoma

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Key Words

Central nervous system involvement · Metastatic sarcoma · Pediatric patients

Abstract

Objectives: To summarize and analyze the experience in CNS involvement (CNSI) in children with sarcomas treated in the above-mentioned institutions. ***Patients and Methods:*** From 1990 to 2001, all medical charts were retrospectively reviewed: 19 sarcoma patients (12 boys and 7 girls) were diagnosed with CNSI (4 osteogenic sarcomas, 11 Ewing sarcomas, 2 rhabdomyosarcomas, 1 alveolar soft part sarcoma and 1 mesenchymal chondrosarcoma). Mean age of all patients at the time of initial diagnosis was 14.9 years (range: 4–24 years), mean age at the time when CNSI was diagnosed was 16.9 years (range: 5.5–27 years). ***Results:*** The frequency of CNSI among our patients was 6.17%. The following symptoms and signs (sometimes combined) presented: headache (10 patients), nausea and vomiting (6 patients), seizures (11 patients) and focal neurological signs (9 patients). The mean duration of time elapsed since diagnosis of CNSI till death or last follow-up was 5.2 months (SD: ±5.7 months). Four patients received chemotherapy (CT) alone, 8 CT and radiotherapy (RT), 2 RT alone, 3 supportive treatment only, 1 CT and surgery and 1 surgery alone. Sixteen patients died; there was no significant difference in the duration of survival between those who were treated with RT or surgery (mean ± SD: 6.77 ± 6.56 months) and those who received only CT or supportive treatment (mean ± SD: 2.60 ± 2.94 months) ($p = 0.07$). Brain disease was the main cause of death in all but 1 patient who died 4 days after autologous bone marrow transplantation from uncontrolled sepsis. In 16 patients, CNSI was part of a metastatic disease. ***Conclusions:*** Among children with sarcoma, CNSI is encountered in 6.17% of cases. More effective therapy has to be developed in order to improve their outcome.

Introduction

Recent advances in the management of pediatric patients with various types of sarcoma have enabled the achievement of survival in a majority of affected children. Current survival rates for children with osteogenic sarcoma (OS) are about 65% [1], being even higher (75%) in children with Ewing's sarcoma (ES) [2, 3] and soft tissue sarcoma [4–8]. The major prognostic determinant in patients with sarcomas is the metastatic status at the time of

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Table 1. Patient characteristics and disease status

Patient No.	Age years	Sex	Histological type of sarcoma	Location of primary	Metastatic status at the time of initial diagnosis
1	13	M	ES	left proximal femur	no metastasis
2	16.5	M	OS	right tibia	bone marrow, bones, lung
3	8	F	ES	pelvis	no metastasis
4	18	F	ASPS	right posterior thigh	lung
5	14	M	OS	left distal femur	no metastasis
6	19	F	ES	pelvis	bone marrow, bones, lung
7	17	M	OS	left distal femur	lung
8	18	M	ES	multifocal bone	bones
9	16.5	M	ES	right distal femur	no metastasis
10	14	F	ES	right chest wall	no metastasis
11	10.9	M	OS	right proximal humerus	lung
12	24	F	MC	left chest wall	no metastasis
13	21.5	M	ES	multifocal bone	bones
14	20	F	ES	pelvis	no metastasis
15	4	M	ES	pelvis	no metastasis
16	12	M	ES	left proximal femur	no metastasis
17	20	F	RMS	left maxillary sinus	bone marrow, bones
18	10	M	RMS	left foot	no metastasis

Age at diagnosis is given. ASPS = Alveolar soft part sarcoma; MC = mesenchymal chondrosarcoma.

diagnosis [3, 6–9]. Patients diagnosed with localized disease usually have a favorable prognosis, while those who present with widespread metastases (most commonly to lungs and bones) usually do badly and, ultimately, succumb to their disease. Using modern treatment modalities of combinations of surgery, radiotherapy and chemotherapy, including high-dose chemotherapy with stem cell support, survival may be significantly prolonged in many patients and, in selected cases, even cure may be achieved [5].

Brain metastases are usually diagnosed in the context of widespread disease, during the late phases when a child has already received multiple courses of chemotherapy, often was treated with radiotherapy and has undergone at least one surgical intervention [10–13]. Such children are usually in a very poor general condition, vulnerable to the possible complications of additional therapeutic interventions. This makes it very difficult to determine optimal and efficacious treatments.

We present multi-institutional experiences in managing pediatric patients with various types of sarcoma who developed brain metastases.

Patients and Methods

Four hundred and eleven patients were diagnosed with various types of sarcoma in the years between 1990 and 2001 in three hospitals in Israel: The Rambam Medical Center in Haifa, the Schneider Children's Hospital in Petach Tikva, and the Hadassah Medical Center in Jerusalem. Of those 411 patients, 236 children were diagnosed with bone sarcoma and 175 with soft tissue sarcomas. A total of 18 (4.3%) patients were diagnosed with brain metastases during their disease. The incidence of brain metastases was 5.9% (14/236) for children diagnosed with bone sarcomas and 2.28% (4/175) for those diagnosed with soft tissue sarcomas. The mean age of all patients with brain metastases was 15.4 years (range 4–24 years). There were 11 boys and 7 girls. The patients suffered from the following diseases: 10 patients from ES, 4 patients from OS, 2 patients from rhabdomyosarcoma (RMS), 1 from alveolar soft part sarcoma and 1 patient from mesenchymal sarcoma (table 1). Ten patients had no metastatic disease at the time of initial diagnosis while 8 patients had metastatic spread. Of these 8, 3 had lung metastases only, 2 were diagnosed with bone metastases only, 2 had simultaneous involvement of lungs, bones and bone marrow, and 1 patient had metastatic disease in bone and bone marrow.

All patients were initially treated according to international therapeutic protocols for these disease. Routine follow-up consisted of chest CT, technetium bone scan and MRI of involved parts of the musculoskeletal system. Brain imaging with CT or MRI was performed only when suspicious symptoms or signs raised a possibility of CNS involvement in the pathological process. A diagnosis of CNS involvement was established on the basis of a thorough neurological examination coupled with CT or MRI of the brain. Brain metastasis

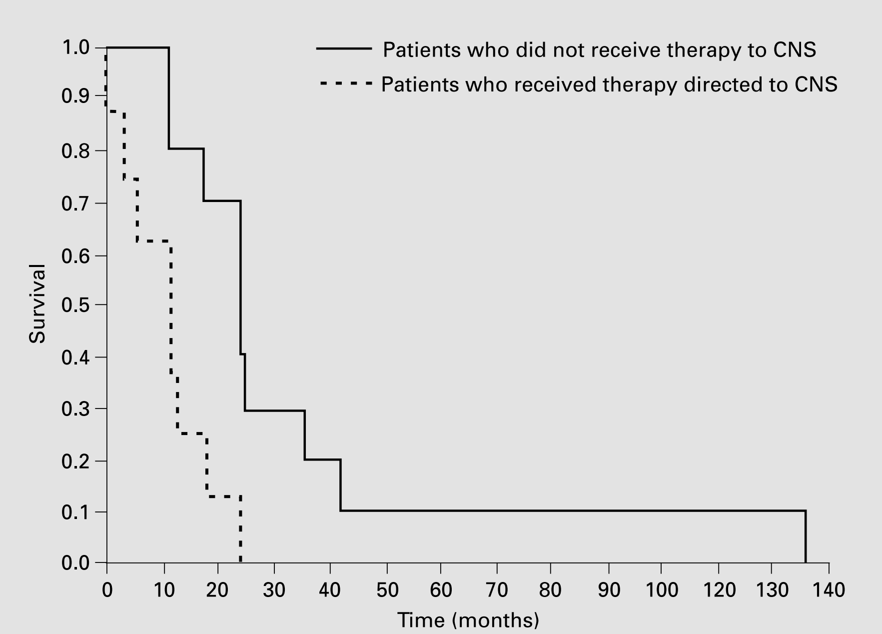

Fig. 1. Mean duration of time elapsed from the diagnosis of sarcoma until diagnosis of CNS involvement (p = 0.037).

was diagnosed only if it was located within the brain parenchyma. CNS involvement per continuum from the skull's primary disease was not recognized as metastatic brain disease.

Statistical Analysis

The survival time technique was used to analyze data of mortality. Survival probabilities of event (death) were estimated using the Kaplan-Meier method [14]. Survival curves were compared using the log-rank test. The significance level of $p < 0.05$ was used in all analyses.

Results

Eighteen patients developed metastatic disease to the brain. The mean age of the patients when CNS involvement was diagnosed was 17.4 years (range, 5.5–27 years).

All children had some neurological symptoms and/or signs, which enabled us to suspect CNS involvement and served as indications for performance of either CT or MRI studies. Eleven patients complained of headache, 6 suffered from nausea and/or vomiting, 5 had complaints of progressive visual decline, 11 patients had generalized or focal seizures as a part of the clinical picture of brain metastases and 10 suffered from focal neurological deficits. Fifteen children were diagnosed as having supratentorial metastatic disease, 2 subtentorial, and 1 patient had both supra- and subtentorial involvement. Seven patients had solitary metastatic spread and 11 had more than one metastasis.

For the 10 patients who had localized disease initially, the mean time that elapsed from the time of initial diagnosis until the establishment of CNS involvement was 34.3 months (SD ± 33.6 months; range, 12–126 months). For the 8 children who had metastatic disease from the beginning, this interval was 11.1 (SD ± 7.8 months; range, 0–24 months). This difference was statistically significant (p = 0.037; fig. 1).

The disease status of the children at the time of diagnosis of brain metastases was as follows: 3 patients were in complete remission and CNS was the only site of metastatic spread; 13 patients had clinically and radiologically evident metastatic disease, with a majority having lung metastases with or without involvement of other sites; 1 patient suffered from local recurrence and the metastatic status of 1 patient was unreported.

The management of brain metastatic disease was individualized and depended on the general condition of the patient. Three patients received supportive treatment only, 4 patients were given chemotherapy alone, 2 patients received radiotherapy as a sole mode of treatment, 7 others were treated with a combination of chemotherapy and radiotherapy, 1 patient underwent surgery alone

Table 2. Management of the patients

Patient No.	Treatment before diagnosis of brain metastasis	Disease status at time of diagnosis of brain metastasis	Location of brain metastases	Age years	Treatment of brain metastases	Duration of follow-up months	Outcome
1	VAC + VP-16 + Ifosfomide + surgery + Rtx	bones, lungs	posterior fossa	16	Rtx: 40 Gy + Navalbine	4	DOD
2	Platinol + HD-MTX + Adriamycin	as at initial diagnosis	left frontoparietal, right temporoparietal	16.5	Ctx	4	DOD
3	VAC + VP-16 + Ifosfomide + Rtx	CR local	supratentorial	10	Rtx: 40 Gy + Ctx + ABMT	0.25	died 4 days after ABMT
4	Ctx + surgery + Rtx	lung	posterior fossa	18.3	surgical removal	24	DOD
5	Platinol + HD-MTX + Adriamycin + surgery	lung, bones	left parietal lobe	15	surgical removal + Ctx	4	DOD
6	VAC + VP-16 + ifosfomide; topotecan + Cytoxan, ABMT + Rtx	lung, bones	right internal capsule	21	gemcitabine	1	AWD
7	Ctx + surgery	lung	left parietal lobe	18.5	supportive treatment only	3	DOD
8	VAC + VP-16 + Ifosfomide	bones, lungs, bone marrow	right parietal, right occipital, mesencephalon, lepto-meningeal dissemination	19	Cytoxan + topotecan + MTX + Rtx	13	DOD
9	VAC + VP-16 + Ifosfomide + Rtx	lung	right parietal, temporo-occipital	27	Cytoxan + topotecan + vincristine + Rtx	8	AWD
10	VAC + VP-16 + Ifosfomide + Rtx	local recurrence	left occipital	16.1	supportive treatment only	0.5	DOD
11	Platinol + HD-MTX + Adriamycin + surgery	CR local	left temporal, right parietal	12	gemcitabine, Ifosfomide	1	DOD
12	Ctx + radiotherapy + ABMT	bones, lungs	posterior fossa + brain-stem + facial canal + Meckel's cave	26	Cytoxan + topotecan + Rtx	7.5	DOD
13	VAC + VP-16, Cytoxan + topotecan	bones	cavernous sinus, suprasellar cyst	22	VAC + radiotherapy	1.5	AWD
14	VACA, JET, cisplatin + Adriamycin + Rtx	bones, lung	thalamus, left basal ganglia	23.5	supportive treatment only	0.25	DOD
15	VAC + VP-16 + Ifosfomide + Rtx	bones, lungs	temporal	5.5	Cytoxan + topotecan + vincristine	8.5	DOD
16	VAC + VP-16 + Ifosfomide + surgery	bones, lungs	right occipital lobe	14	Rtx	2	DOD
17	Ctx		right and left parietal	21	Rtx	6	DOD
18	VAC + VP-16 + Ifosfomide	CR local	left cerebellar, right and left parietal	11	Rtx + Ctx	2	DOD

Age is given at the time brain metastasis is diagnosed. Rtx = Radiotherapy; ABMT = antologous bone marrow transplantation; Ctx = chemotherapy; CR = complete response; DOD = died of disease; AWD = alive with evidence of disease; MTX = methotrexate.

and 1 patient surgery combined with subsequent chemotherapy. All but 3 patients died despite treatment. Three patients are alive with evidence of disease at the time of writing (table 2).

For the whole group, the mean duration from the time of diagnosis of CNS involvement to the time of death or last follow-up is 5.03 months (SD ± 5.8 months). There was neither a significant difference in survival (from the time brain metastasis was diagnosed) between children who received direct CNS therapy (mean ± SD: 6.57 ± 6.85 months) and those who were treated with chemotherapy alone or only with supportive treatment (mean ± SD:

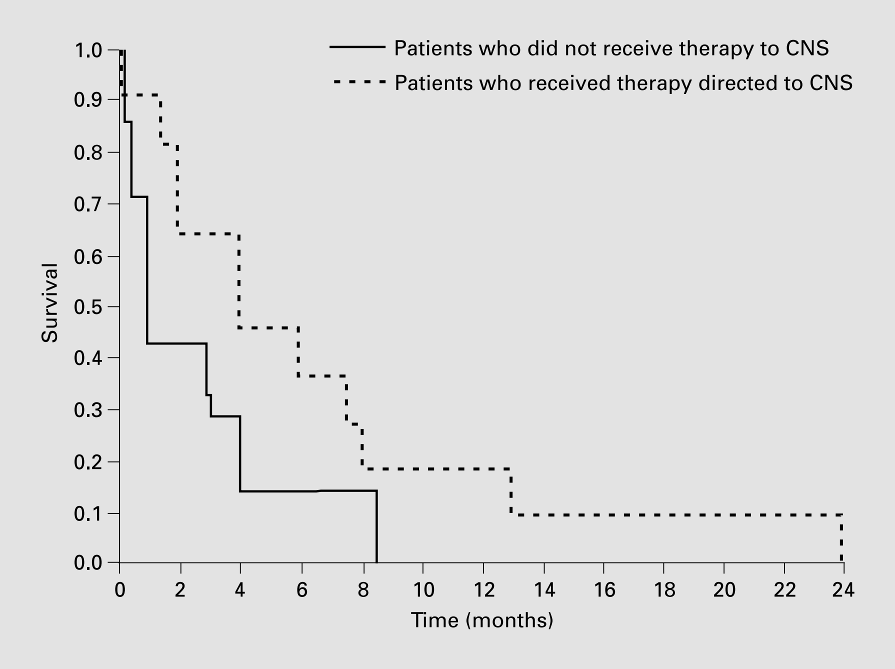

Fig. 2. Mean duration of time elapsed from the diagnosis of CNS disease until death or last follow-up (p = 0.138).

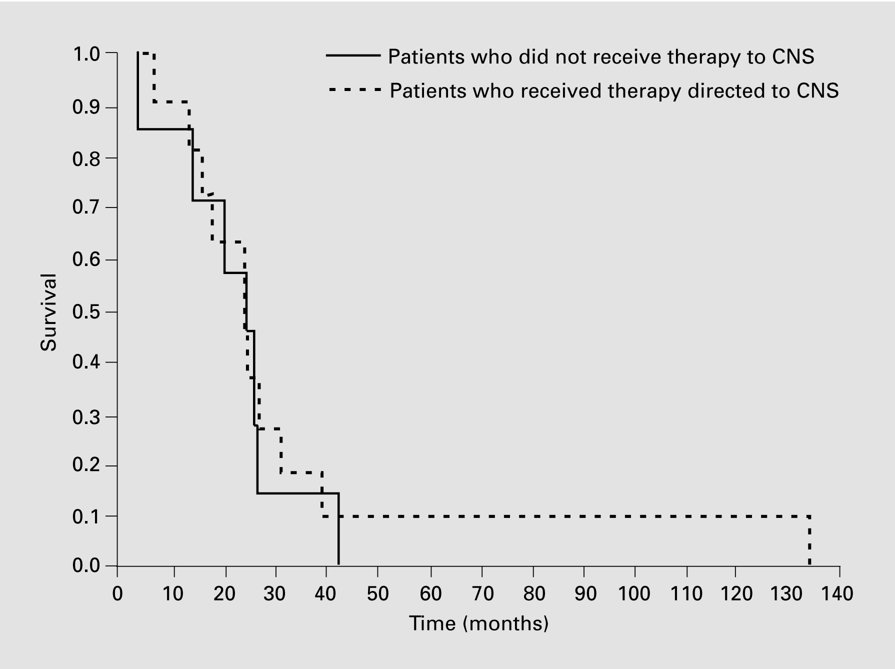

Fig. 3. Mean duration of time elapsed from the diagnosis of sarcoma until death or last follow-up (p = 0.65).

2.6 ± 2.94 months; p = 0.138; fig. 2), nor between these two groups when survival was calculated from the time of initial diagnosis of sarcoma until death or last follow-up (mean ± SD: 22.7 ± 11.8 and 33.1 ± 34.6 months, respectively; p = 0.65; fig. 3).

Discussion

The development of brain metastases is an ominous sign in children suffering from cancer. Usually, metastatic disease to the CNS is an event heralding approaching death. Graus et al. [15] found brain metastases in 31 of

139 patients under 21 years of age with solid tumors (excluding primary CNS tumors and brain lymphoma), using CT of the brain or postmortem examination. In patients younger than 15 years, OS and RMS were the two most common primary tumors causing brain metastases. In patients aged 15–21 years, germ cell tumors were the main cause of metastatic involvement of the CNS. The authors noted that in 90% of patients brain metastases developed when pulmonary metastatic disease had already been established.

There are two possible mechanisms leading to a spread of sarcoma to the brain. The first is a hematogenous spreading of tumorous cells. In such cases, metastases can usually be detected within the brain parenchyma, and sometimes there are several synchronous metastatic loci. The second way of CNS involvement is direct expansion of a tumor into adjacent brain tissue from metastatic loci in skull bones, such as the calvaria or sphenoid bone.

There have been several attempts to analyze the data in order to decide whether early recognition of metastatic involvement of the CNS could potentially lead to a better survival of these patients. Parasuraman et al. [16] analyzed their experience with 419 RMS and 335 ES patients. Totally, 21 of 754 (2.8%) patients were diagnosed with brain metastases. Of those, 10 of 419 (2.4%) suffered from RMS and 11 of 335 (3.3%) suffered from ES. The median time elapsed from initial diagnosis to the appearance of brain metastases was 12 months for patients with RMS and 22 months for patients with ES. This difference was statistically significant. Of these 21 patients, 6 children received either supportive treatment or chemotherapy only. All 6 died within 21 days. Another 15 patients were treated with some therapy directed to their brain disease (surgery ± radiotherapy ± chemotherapy). Nevertheless, all but 1 died within 1 day to 21 months. The median duration of survival after diagnosis of brain metastases was 2.7 months, and there was no significant difference in survival between the two groups ($p = 0.134$ from the date of primary diagnosis and $p = 0.6$ from the date of diagnosis of brain metastasis). The authors conclude that routine neuroimaging studies are not warranted at the time of initial diagnosis in children with RMS or ES since: (1) these patients rarely have CNS involvement at the start of their disease, (2) brain metastases, when present, are usually accompanied by neurological signs and symptoms, (3) the absolute majority have clinically evident widespread disease at the time of brain involvement, and (4) early detection of brain metastases does not alter the grave outcome. In our study also, we were not able to demonstrate any significant difference in survival between children who received only chemotherapy or supportive treatment and patients who were treated by radiotherapy and/or surgery.

The fact that aggressive methods of treatment of CNS involvement do not prolong survival in such patients does not preclude approaching these children with this strategy in selected cases. It has been shown [17–19] that some children may benefit from surgical removal of isolated brain metastases, especially when there is a reasonable time span for survival, and the primary aim of this intervention is improving the remaining life of a child.

Marina et al. [18] published their experience with children suffering from OS. Thirteen of 254 (5.11%) patients were diagnosed with brain metastatic disease. All these children had neurological symptoms or abnormal neurological examinations, and 11/108 (10.1%) patients diagnosed with recurrence during the 1st year from initial diagnosis developed brain metastases. In contrast, only 2 of 40 (5%) patients who had longer progression-free survival ultimately developed CNS involvement. Again, the authors concluded that early detection of brain metastatic disease is unlikely to affect outcome in the absence of new therapies. However, it is maybe advisable to perform CT or MRI of the brain for patients with OS who have metastatic disease at the time of initial diagnosis or who develop recurrence during the 1st year of disease.

Spunt et al. [20] analyzed the usefulness of routine brain imaging in patients with metastatic RMS. According to the IRS-IV protocol, all patients with metastatic RMS at the time of initial diagnosis are advised to undergo CT or MRI of the brain. A total of 56 of 100 eligible children in the Spunt study had their brain imaged by either CT or MRI scans. Only 7 of these 56 (12.5%) patients had abnormal scans. Of these, 4 children had symptoms or signs of brain involvement, but none had any metastatic CNS disease per se. Three other patients had no clinical suspicion of brain disease before brain imaging but had actual brain disease verified on CT or MRI. In 2 of these 3 patients, signs of brain metastatic disease were overlooked on skull X-ray and bone scan with ^{99m}Tc. The 3rd patient had a primary tumor extended to the spinal canal with signs of leptomeningeal spreading correctly diagnosed only on postmortem examination. Based on these results, the authors concluded that routine brain imaging in children with metastatic asymptomatic RMS not arising in the head or neck region is unnecessary. This holds especially true when taking into account the exceptional rarity of brain metastases at the time of initial diagnosis of metastatic RMS.

Randomized trials have not been published comparing two different strategies that could be applied to patients with sarcoma metastatic to the brain: supportive treatment only versus surgery or radiotherapy directed specifically to brain involvement. Many of these patients are in extremely poor condition, making an aggressive approach unrealistic, so there is an intentional bias towards treatment with more 'radical' methods in those patients whose general condition allows such therapy to be performed.

We are aware that our study is not without limitations. Firstly, this study is retrospective in nature and is not devoid of the drawbacks of any retrospective study. In some cases, it was impossible to extract all the necessary information from the medical charts, e.g. we were unable to collect data on the metastatic status of 1 patient at the time of CNS diagnosis. In addition, we did not always know why a specific mode of therapy was chosen. Secondly, a truly objective comparison of two study groups is very difficult, due to the possible tendency to operate on those patients who have isolated brain metastasis and are in a good general condition. Therefore, these patients, from the outset, had better chances for prolonged survival than those with multiple metastases and/or in a poor performance status. Hence, the bias when survival results are compared is not excluded.

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